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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/484,121 | 01/13/2000 | Ralf Reiner Schumann | 0107-020P/GPK | 9305 |

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| EXAMINER |
|---|
| KAM, CHIH MIN |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1653 | 28 |

DATE MAILED: 04/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application N . | Applicant(s) | |
|---|---|---|---|
| | 09/484,121 | SCHUMANN ET AL. | |
| | Examin r | Art Unit | |
| | Chih-Min Kam | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *12-18,22,23 and 28-33* is/are pending in the application.

4a) Of the above claim(s) *12-18, 22, 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Status of the Claims*

1. Claims 12-18, 22, 23 and 28-33 are pending.

Applicants' amendment filed on January 22, 2003 (Paper No. 27) is acknowledged, and applicants' response has been fully considered. Claims 28 and 31-33 have been amended, and claims 12-18, 22 and 23 are non-elected inventions, thus withdrawn from consideration. Therefore, claims 28-33 are examined.

### ***Objection Withdrawn***

2. The previous objection of claims 28, 31 and 32 is withdrawn in view of applicants' amendment to the claim in Paper No. 27.

### ***Rejection Withdrawn***

### *Claim Rejections - 35 USC § 112*

3. The previous rejection of claims 28-32, under 35 U.S.C.112, second paragraph, is withdrawn in view of applicants' amendment to the claim and applicants' response at page 2 in Paper No. 27.

### *Claim Objection*

4. Claim 32 is objected to because of the misspelling word "bacteriocidal".

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 32 and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 32 and 33 are directed to a method for treating septicemia comprising administering a hybrid of LBP and a lipopolysaccharide binding site of BPI (bactericidal/permeability increasing protein), a hybrid of LBP and a lipopolysaccharide binding site of LALF (limulus ant-lipopolysaccharide factor), or, a mutant of LBP. The specification indicates that murine LBP at high dosage suppresses the production of TNF-α, suppresses the liver damage induced by LPS and reduces the lethality of animals in a LBP septicemia model (See drawings), and LBP mutants are used as therapeutic agents for treatment of septicemia (page 2, lines 7-9). However, the specification does not identify any mutants and hybrid proteins of LBP nor discloses how to obtain these mutants and hybrid proteins of LBP, and how to use these proteins in the treatment of septicemia. There is no structural or functional identification of the mutants or hybrid proteins of LBP. Without guidance on structure to function/activity of the mutants or hybrid proteins of LBP, one skilled in the art would not know which region of the protein is essential for function/activity and how to identify a functional peptide. The lack of a structure to function/activity relationship of the protein and the lack of representative species for the mutants or hybrid proteins of LBP as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

6. The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

***Claim Rejections - 35 USC § 112***

7. Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 is indefinite because of the use of the term "LBP comprises one or more point mutations". The term "LBP comprises one or more point mutations" renders the claim indefinite, it is unclear where is the mutation in the sequence of LBP, and what mutation is intended.

***Claim Rejections - 35 USC § 102***

8. Claims 28, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Scott *et al.* (WO 94/25476).

Scott *et al.* teach a pharmaceutical composition comprising a therapeutically effective amount of a BPI variant, a LBP variant, or an LBP-BPI chimera and a pharmaceutically acceptable carrier, and a method of treating endotoxin-related disorders such as sepsis and septic shock using the composition (page 2, line 34-page 3, line 4; pages 13, 14, 18, 22, 23, 25; Tables 3-6). The composition contains a LBP mutant such as $L_{(S77->K)(R86->K)\ (S96->K)\ (L118->K)(R126->K)}$ (NCY141 in Table 3) which has one or more point mutations (claim 33), or a LBP-BPI chimera such as $B_{1-200}\ L_{199-456}$ (NCY 104 in Table 3) which is a hybrid protein of LBP (L) and BPI (B) and has lipopolysaccharide binding site (N-terminal region of BPI; claim 32). The LBP mutant

or the hybrid protein of LBP and BPI is a LBP (claim 28) since neither the claim nor specification specifically defines the LBP.

In response, applicants indicate Scott *et al.* describe BPI inhibits LPS-mediated activity, whereas LBP stimulates LPS-mediated activity, thus, Scott proposes the development of LBP variants and LBP-BPI chimeras that possess an LPS binding activity and a longer half-life than native LBP in order to inhibit LPS-mediated activity; while the present invention shows LBP inhibits LPS-mediated activity in vitro and in vivo and can be used as a therapy for LPS-ailments (page 3 of the response). The response has been fully considered, however, the argument is not persuasive because Scott *et al.* disclose the LBP-BPI chimeras have LPS binding activity and inhibit LPS-mediated activity as indicated in the claimed invention, thus the claims are anticipated by the reference.

9. Claims 28 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Heavner *et al.* (WO 95/08560).

Heavner *et al.* teach a pharmaceutical composition comprising a peptide derived from a portion of amino acids 95-104 of LBP such as Arg-Lys-Ser-Phe-Phe-Lys-Leu-GlN-Gly-Ser-Phe-Asp-Val-Ser-Val-$NH_2$ (SEQ ID NO:1) and its variants (SEQ ID NO:2-64, see pages 9-12, 21-22 and Examples 1-9), and a method for treating sepsis caused by gram-negative bacteria using the composition (page 5, line 12; claims 28 and 33). The LBP-derived peptides are LBP variants which are encompassed by LBP since neither the claim nor specification specifically defines the LBP.

In response, applicants indicate Heavner *et al.* teach the use of LBP-derived peptides for treating sepsis by inhibiting the LBP-LPS interaction, however, the reference does not teach the

use of the entire protein in the treatment (pages 3-4 of the response). The argument is not persuasive because neither the specification nor the claim specifically defines LBP as the entire protein of LBP, thus, a LBP peptide having the LPS-binding activity is encompassed by LBP.

***Claim Rejections - 35 USC § 102&103***

10. Claims 29-31 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Scott *et al.* (WO 94/25476).

Scott *et al.* teach a pharmaceutical composition comprising a therapeutically effective amount of a BPI variant, a LBP variant, or an LBP-BPI chimera and a pharmaceutically acceptable carrier, and a method of treating endotoxin-related disorders such as sepsis and septic shock using the composition (page 2, line 34-page 3, line 4; pages 13, 14, 18, 22, 23, 25; Tables 3-6), where LBP can be human, mouse or rabbit LBP in the LBP-BPI chimera (page 11, lines 1-5; page 18, lines 5-13; Fig. 5; claims 29-31). Claims 29-31 are anticipated as the construct recited in the claimed process would have been anticipated by teaching of producing chimeras of LBP and BPI (See page 11, lines 1-5; page 18, lines 5-13). In the alternative that it would have been obvious if not anticipated that the teaching regarding chimeric constructs would have motivated one of ordinary skill in the art to have made substitutions of rabbit, human or mouse (murine) LBP (See Fig. 5 which discloses various LBPs). The practice of the process with these constructs would have resulted in the claimed invention which was at least obvious if not anticipated from the cited reference. The chimera of LBP and BPI is a LBP since neither the claim nor specification specifically defines the LBP. Please see paragraph 7 on the response to applicants' argument.

***Conclusion***

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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April 9, 2003

Christopher S. F. Low
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